Randomised comparison of the effects of nicardipine and esmolol on coronary artery wall stress: implications for the risk of plaque rupture

M J A Williams, C J S Low, G T Wilkins, R A H Stewart

Abstract

Objective—To determine whether the β blocker esmolol reduces coronary artery wall stress more than the short acting dihydropyridine calcium antagonist nicardipine.

Design—Randomised double blind placebo controlled trial.

Setting—Tertiary cardiology centre.

Patients—Patients with coronary artery disease.

Interventions—20 patients were randomised double blind to an infusion of nicardipine (n = 10) or esmolol (n = 10) titrated to reduce systolic blood pressure by 20 mm Hg.

Main outcome measures—Peak systolic wall circumferential stress.

Results—Esmolol reduced peak coronary stress by a mean of 0.17×10^6 dyn/cm^2 (95% confidence interval (CI) 0.14 to 0.21×10^6 dyn/cm^2) compared with a reduction of 0.07×10^6 dyn/cm^2 (95% CI 0.05 to 0.10×10^6 dyn/cm^2) after nicardipine. Peak systolic radius was reduced by 0.04 mm (95% CI 0.03 to 0.06 mm) after esmolol compared with an increase of 0.08 mm (95% CI 0.05 to 0.10 mm) after nicardipine. Heart rate increased by 11.5 beats/min (95% CI 6.9 to 16.2 beats/min) after nicardipine and decreased by 5.3 beats/min (95% CI 1.9 to 8.6 beats/min) after esmolol.

Conclusions—Intravenous esmolol is more effective than nicardipine at reducing circumferential coronary artery wall stress.

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It is established that β blockers reduce mortality following myocardial infarction.[1] In contrast there is controversial evidence that short acting dihydropyridine calcium antagonists do not decrease[2 3] and may even increase the risk of cardiovascular events.[4-6] The pathophysiological mechanisms which might account for different rates of ischaemic coronary events with these two drug classes are uncertain. Proposed mechanisms for the possible adverse effects of calcium antagonists include sympathetic activation, proischaemia, negative inotropy, and reflex tachycardia.[4 7 8]

Plaque rupture is the most common initial event in unstable angina and myocardial infarction.[9] The risk of plaque rupture is determined by the intrinsic properties of the plaque and extrinsic forces acting on it.[10] It is possible that β blockers and dihydropyridine calcium antagonists, while both lowering blood pressure, have different effects on coronary artery wall stress, a possible determinant of plaque rupture.[11] In this study we test the hypothesis that, for an equivalent reduction in systolic blood pressure, the β blocker esmolol reduces coronary artery wall stress more than the short acting dihydropyridine calcium antagonist nicardipine.

Methods

STUDY PATIENTS

Eligible patients had single vessel coronary artery disease, were scheduled to have elective coronary angioplasty, and had minimal disease of the proximal left anterior descending or left circumflex coronary artery. Patients were excluded if there were contraindications to receiving nicardipine or esmolol, including asthma, severe valvar disease, congestive heart failure, and impaired hepatic or renal function. Vasoactive drugs were withheld for at least 24 hours before the investigation. Patients were randomised after a successful baseline intravascular ultrasound study had been completed. Written informed consent was obtained from all participating patients and the study was approved by the regional health authority ethics committee.

CATHETERISATION PROCEDURE

After administration of 10 000 U heparin, coronary angiography was performed through the right femoral artery using 6 French diagnostic catheters. Nitrates or other non-study vasoactive drugs were not given before or during the research protocol. An 8 French left Judkins type guiding catheter was then used for insertion of either a 3 French or a 3.5 French, 30 MHz intravascular ultrasound (IVUS) imaging catheter (Boston Scientific, Watertown, Massachusetts, USA) into the proximal left anterior descending or proximal circumflex coronary artery. Arterial pressure was measured with a 2 French micromanometer (Millar Mikro-Tip SPC-320, Millar Instruments, Houston, Texas, USA) inserted from the left femoral artery through a 6 French left diagnostic Judkins type catheter, with its tip located adjacent to the left main coronary artery ostium.

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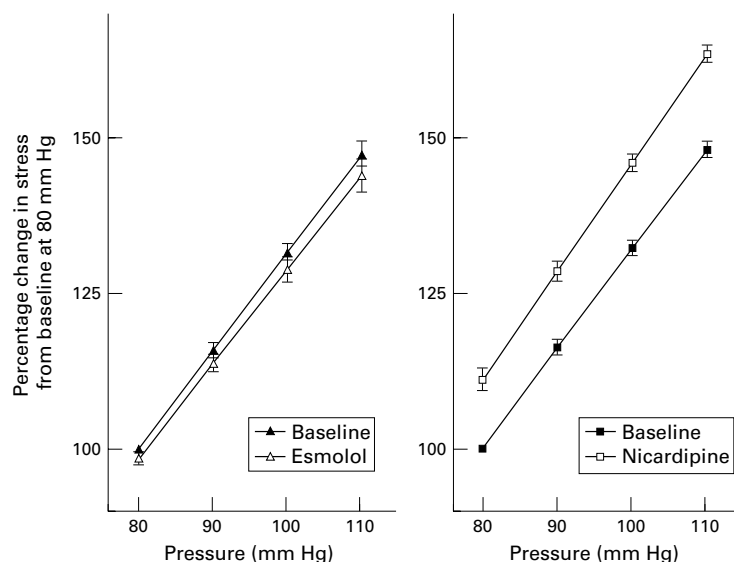michael.williams@
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Figure 1   Relation between circumferential wall stress and arterial pressure before and after esmolol (left) and nicardipine (right). Results are presented as means with SEM. Circumferential wall stress is expressed as the percent change from baseline stress estimated at 80 mm Hg. Esmolol reduced coronary artery stress (p = 0.024) while nicardipine increased it (p = 0.001).

The IVUS imaging catheter was positioned in the proximal coronary artery at a site where there was homogeneous circumferential vessel wall thickening without eccentric plaque formation, as close as possible to the centre of the vessel and away from side branches and bifurcations. Images were optimised by use of compression, time gain compensation, and post-processing controls to identify the lumen–intima interface and the media–adventitia interface. The guiding catheter was withdrawn from the ostium of the left main coronary artery to avoid damping coronary pressure. Baseline images were recorded approximately three minutes after the IVUS imaging catheter was placed in the study artery. The coronary artery pressure waveform and coincident arterial images were acquired using a Hewlett-Packard Sonos 100 IVUS machine and recorded on Super-VHS videotape for subsequent analysis. The ECG and coronary pressures were recorded as a digital file using a MacLab 8/s hardware unit (AD Instruments, Castle Hill, NSW, Australia).

STUDY PROTOCOL

Patients were randomised blockwise to treatment allocation using a random number list. The allocation schedule was kept in a numbered series of sealed opaque envelopes. All patients randomised completed the study protocol. Drug infusions were prepared by staff not involved with the trial and were given double blind. After the baseline intravascular ultrasound study, patients received an infusion of either esmolol (500 μg/min) or nicardipine (500 μg/min) to reduce the systolic blood pressure by approximately 20 mm Hg. After achieving the target blood pressure reduction (nicardipine, 5.8 (2.0) minutes; esmolol, 11.5 (2.9) minutes (mean (SD)) the drug infusion was continued to maintain a steady state for

two minutes, and a repeat ultrasound study was performed in the same position as the baseline study.

DATA ANALYSIS

The intravascular ultrasound images were analysed off-line to determine coronary artery luminal area and wall thickness by a single observer blinded to treatment allocation. Video frames were digitised using the built in digitise of a PowerMac 8500 computer and measured using NIH Image 1.60, a public domain program from the US National Institutes of Health. Peak systolic, late systolic, early diastolic, mid-diastolic, and late diastolic images and their simultaneously acquired pressures were measured at matching time intervals for three sequential cardiac cycles. The luminal area was determined by tracing the lumen–intima interface for each of these phases of the cardiac cycle and the results recorded as the mean of three cardiac cycles. Wall thickness was measured as the distance from the lumen–intima interface to the media–adventitia interface.[12] This measurement does not include the thickness of the arterial adventitia, which represents a small proportion of the arterial wall thickness in an atherosclerotic coronary artery.[13] Five measurements of wall thickness were made at peak systole and averaged for three cardiac cycles. Wall thickness for other phases of the cardiac cycle was calculated by assuming the vessel wall was incompressible and that wall volume remained constant through the cardiac cycle.[14 15] Heart rate was calculated from the ECG after the measurement of all ultrasound images to maintain blinding of treatment allocation.

CALCULATIONS

Measurements of arterial area (A) were used to derive the inner arterial radius (r):

$$r = \sqrt{\frac{A}{\pi}} \qquad (1)$$

Circumferential wall stress (σ) was calculated by the following formula:

$$\sigma = \frac{P \times r}{h} \qquad (2)$$

where P is arterial pressure, r is the arterial radius, and h is arterial wall thickness.

Pressure–stress relation

To assess the effects of drug treatment on coronary stress while controlling for the effects of blood pressure, a pressure–stress relation was calculated before and after drug treatment. The method of calculating the pressure–stress relation has been reported.[13] A mathematical model was used to fit arterial pressure and lumen area data, and this model was used to derive pressure–stress curves which would permit comparison of the effects of study drugs on coronary stress over a common range of pressures. This allows direct comparison of the effects of each drug on coronary stress,

Table 1 Baseline characteristics of the patients

	Nicardipine (n=10)	Esmolol (n=10)
Demography		
Age (years) (mean (SD))	54.3 (8.8)	59.0 (5.9)
Male/female	8/2	6/4
Risk factors		
Hypertension	4	2
Hypercholesterolaemia	8	4
Diabetes	3	1
Previous drug treatment		
β Blocker	8	7
Calcium antagonist	6	7

mediated by their effect on arterial radius independent of passive changes in arterial radius related to changes in blood pressure.

Arterial pressure and area data points were plotted and fitted with least squares regression using the arctangent function described by Langewouters and colleagues.[16]

$$A = \alpha \left[\frac{1}{2} + \frac{1}{\pi} \tan^{-1} \left(\frac{P - \beta}{\gamma} \right) \right] \qquad (3)$$

where A is arterial area, P is arterial pressure, and α, β, and γ are three optimal fit parameters.

All individual pressure–area data fit this arc tangent model with $R^2 > 0.99$. The individual pressure–area functions were then used to calculate pressure–stress curves using equations (1) and (2) for each patient before and after drug treatment. Points on the fitted curves for individual subjects were averaged every 10 mm Hg in the range from 80 mm Hg to 110 mm Hg (this range of pressures included values recorded from all patients) and the group mean values plotted before and after drug treatment (fig 1).

END POINTS

The primary study end point was change in peak circumferential coronary wall stress. The secondary end point was the change in circumferential stress controlled for pressure.

STATISTICS

The sample size calculation was based on the expectation that differences in coronary stress would be related to changes in vessel radius,

assuming similar wall thickness and blood pressure. Intracoronary nicardipine has been reported to increase vessel area by 11%,[17] which represents an increase in vessel radius of approximately 5%. For the primary end point of coronary circumferential stress the study (two groups of 10 patients) had a 95% power of detecting a difference in circumferential stress of 5% (SD 3%), assuming a two sided type I error level of 0.05. The statistical analysis was performed with SPSS. The results for the two treatment groups were compared with unpaired Student's *t* test for normally distributed variables and the Wilcoxon rank sum test for other variables. Fisher's exact test was used for categorical variables. The pressure–stress curves generated at baseline and after drug administration were compared with repeated measures analysis of variance. Measurement variability was assessed using the method of Bland and Altman[18] and was expressed as the mean (SD) of the differences in measurements. The effect of treatment on outcome measures is presented as mean change from baseline and 95% confidence interval (CI).

Results

There were 39 patients screened for participation in the study. Of these, 16 had unsuitable coronary anatomy and three did not have a technically satisfactory baseline intravascular ultrasound study. Twenty patients were randomised to either nicardipine (n = 10) or esmolol (n = 10). The baseline clinical characteristics (table 1) and haemodynamic measurements (table 2) were similar for each treatment group. Intravascular ultrasound studies were performed in the proximal left anterior descending artery in 14 patients (nicardipine 7, esmolol 7) and the proximal left circumflex artery in six patients (nicardipine 3, esmolol 3). Intravascular measurements of systolic arterial area, wall thickness, circumferential stress, and coronary stress index were similar for the two treatment groups at baseline (table 2).

Changes in heart rate and arterial indices are presented as the mean change from baseline in

Table 2 Baseline haemodynamics and arterial measurements

	Nicardipine (n=10)	Esmolol (n=10)	p Value
Haemodynamics			
Systolic blood pressure (mm Hg)	136.5 (21.8)	141.4 (22.3)	0.62
Diastolic blood pressure (mm Hg)	83.6 (16.0)	78.3 (9.8)	0.39
Heart rate (beats/min)	70.0 (17.1)	70.9 (9.2)	0.89
Arterial measurements			
Arterial wall thickness (mm)	0.38 (0.14)	0.37 (0.11)	0.91
Peak systolic arterial area (mm^2)	7.86 (2.44)	8.67 (2.68)	0.54
Peak systolic arterial radius (mm)	1.56 (0.26)	1.64 (0.26)	0.49
Peak wall stress (10^6 dyn/cm^2)	0.95 (0.34)	1.00 (0.42)	0.82

Values are mean (SD).

Table 3 Change in heart rate and peak systolic arterial indices with a 20 mm Hg decrease in systolic pressure after nicardipine or esmolol

	Mean change from baseline (95% CI)		Difference (95% CI)	p Value
	Nicardipine (n=10)	Esmolol (n=10)		
Heart rate (beats/min)	11.5 (6.9 to 16.2)	−5.3 (−1.9 to −8.6)	16.8 (11.5 to 22.2)	0.0002
Systolic radius (mm)	0.08 (0.05 to 0.10)	−0.04 (−0.03 to −0.06)	0.12 (0.09 to 0.15)	0.0002
Peak stress (10^6 dyn/cm^2)	−0.07 (−0.05 to −0.10)	−0.17 (−0.14 to −0.21)	0.10 (0.06 to 0.14)	0.0005

Change from baseline = post-drug value − baseline value.

table 3. Analysis of changes in stress independent of blood pressure showed that esmolol minimally decreased coronary artery stress by 2–3% (fig 1). Most of the 18% reduction in peak wall stress after esmolol was caused by the 20 mm Hg decrease in blood pressure. In contrast, after controlling for blood pressure nicardipine increased coronary stress by approximately 10% (fig 1) by causing vasodilatation. This increase offset the reduction in stress related to the 20 mm Hg fall in blood pressure, and the net reduction in peak stress per cardiac cycle was 8% with nicardipine (table 3).

Measurement variability was assessed by measuring 30 randomly selected intravascular ultrasound images for vessel area and 15 images for wall thickness. The mean (SD) difference between two blinded measurements of coronary artery area performed by one observer was 0.02 (0.15) mm^2. The intraobserver difference for measurements of wall thickness was 0.0013 (0.0052) mm.

Discussion

In this study a β blocker and a short acting dihydropyridine calcium antagonist both lowered blood pressure but had different effects on coronary artery circumferential wall stress. Necropsy studies have established that plaque rupture occurs in regions of the arterial wall with high levels of circumferential stress.[11] It is likely that treatment which reduces coronary wall stress will reduce the long term risk of myocardial infarction and sudden death from coronary artery disease. This possibility is consistent with the clearly established benefits of β blockade in reducing reinfarction and death in patients with coronary artery disease.[1] A lesser reduction in coronary wall stress might conceivably contribute to the less favourable effects on cardiovascular events in clinical trials[4–6 19] and case–control studies[20 21] of dihydropyridine calcium antagonists.

Previous investigators have suggested that sympathetic activation associated with reflex tachycardia and raised noradrenaline (norepinephrine) may explain the possible adverse effects of calcium antagonists.[22] However, the precise mechanisms by which these factors increase the risk of cardiovascular events are uncertain. It is possible that sympathetic activation and increased heart rate increase cumulative coronary circumferential stress and therefore the risk of plaque rupture. Studies of materials fatigue show that a stress applied repetitively increases the likelihood of fracture.[23] However, the precise relation between applied stress and cycle number required for plaque fracture in vivo is unknown. A role for heart rate in the risk of plaque rupture is supported by the good correlation between reduction in heart rate and decrease in mortality in patients with coronary heart disease treated with β blockers.[24] In addition, and in contrast to the dihydropyridine calcium antagonists, the non-dihydropyridine calcium antagonists verapamil and diltiazem, which slow heart rate, appear to reduce cardiovascular event rates.[25]

The coronary vasodilator effects of nicardipine acted to increase coronary stress by increasing vessel radius. However, peak coronary wall stress was reduced by nicardipine because the effect of reduction in systolic blood pressure was greater than the direct effect of coronary vasodilatation. This observation suggests that calcium antagonists which do not cause tachycardia may have a favourable effect on coronary artery wall stress. By comparison, β blockers—which do not cause coronary vasodilatation—may be more effective at reducing coronary artery wall stress. In this study homogeneous arterial segments were studied, but both β blockers[26] and dihydropyridine calcium antagonists[17] are known to have similar vasomotor effects in normal and diseased segments of artery.

Changes in coronary wall stress were measured at rest rather than during exercise, when myocardial infarction is more likely to be triggered.[27 28] In addition, the present study assessed acute rather than chronic effects of drug treatment. Reflex tachycardia with dihydropyridines decreases with chronic treatment and is less with long acting dihyropyridine calcium antagonists. The increase in heart rate approximates 3–4% during chronic treatment[22] compared with a decrease in heart rate averaging 14% in 11 randomised trials of long term β blockade.[24] Significant differences in heart rate are therefore likely to persist with long term treatment and during the stress of exercise. However, the effects of long term treatment on coronary wall stress have not been studied and the relation between the acute changes in coronary wall stress measured in this study and the long term risk of plaque rupture is uncertain.

Estimation of mean coronary artery circumferential stress requires simultaneous measurements of arterial area and pressure. These measurements may be influenced by differences between aortic root and proximal artery pressure, vasoconstriction after introduction of the intravascular ultrasound catheter, and axial movement of the imaging catheter.[29] The impact of each of these factors on the measurement of coronary artery wall stress is uncertain. However, the study design—which includes paired measurements before and after drug infusion and double blind random allocation of treatment—makes it unlikely that these factors would bias estimation of the treatment effect.

Several factors not assessed in the current study are likely to influence the risk of plaque rupture, including vessel wall structure, fibrous cap thickness,[11 30 31] lipid content,[32] and local inflammation.[33] Finite element analysis, which assigns mechanical properties to individual elements of arterial wall and plaque based on micromechanical testing, has been used to calculate maximum circumferential stress in vitro.[11 31] Ideally, finite element analysis represents the best method to calculate circumferential stress, given the inhomogeneity of wall composition and mechanical properties in areas of vulnerable plaque. Intravascular ultrasound provides limited information on the distribution of the different components of

atherosclerotic plaque, which has precluded use of the finite element technique in human subjects in vivo.

Peak systolic wall thickness measurements did not include the thickness of the arterial adventitia, which may lead to overestimation of circumferential stress. However, as the adventitia represents a small proportion of the thickness of an atherosclerotic coronary artery, overestimation of circumferential stress is likely to be minimal. In addition, it has been shown that the intima and media bear a greater proportion of total circumferential stress than the adventitia,[11] implying intima–media thickness may be functionally more important when assessing wall stress in an artery with a circumferentially uniform structure.

In this current study we used a thin walled tube model to measure average circumferential stress in segments of artery with symmetrical thickening of the arterial wall rather than diseased segments with asymmetrical plaque. In segments of artery with asymmetrical plaque, mean circumferential wall stress is the same across the section containing plaque and the more normal artery wall, although the distribution of stress across different components of the vessel wall changes. In experimental studies, wall stress is greatest at the margins of the fibrous cap which overlies a lipid pool,[11] and changes in this stress are most relevant to plaque rupture. Plaque cap stress cannot be measured directly with intravascular ultrasound, but in vitro studies have shown a good correlation between maximum stress determined by finite element analysis in asymmetrical vessels and plaque stress, calculated using a cylindrical tube model as the ratio of vessel radius and fibrous cap thickness.[34] The mean reduction in coronary wall stress after esmolol of 0.17×10^6 dyn/cm^2 (approximately 125 mm Hg) was much smaller than the maximum circumferential stress of 4091 (1199) mm Hg calculated at sites of plaque rupture in pathological specimens in vitro.[31] However, it is possible that a small reduction in wall stress over prolonged periods decreases the risk of rupture when a plaque is vulnerable, because of weakening of the fibrous cap, increased lipid content, or local inflammation. Small differences in circumferential wall stress could therefore influence the risk of coronary events during longer term treatment.

It is important to understand the mechanisms by which treatment may influence the likelihood of coronary events. Intravenous esmolol is more effective than nicardipine at reducing circumferential coronary artery wall stress, a possible determinant of the risk of plaque rupture. This mechanism may in part explain the beneficial effects of β blockers in clinical trials of patients with coronary artery disease. Results of large ongoing randomised clinical trials are awaited for reliable determination of the effects of treatment with dihydropyridine calcium antagonists on long term cardiovascular risk.

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IMAGES IN CARDIOLOGY

Visualisation of ablated septal myocardium using myocardial contrast echocardiography in hypertrophic obstructive cardiomyopathy

A 59 year old woman presented with exertional dyspnoea and presyncope. Cross sectional and Doppler echocardiography revealed asymmetric septal hypertrophy, systolic anterior movement of the anterior mitral leaflet, and left ventricular outflow obstruction with a pressure gradient of 140 mm Hg. She was diagnosed with hypertrophic obstructive cardiomyopathy (HOCM), and had been treated with 300 mg of disopyramide per day. Nevertheless, her symptoms and pressure gradient had been refractory, so she was scheduled for percutaneous transluminal septal myocardial ablation (PTSMA). The first major septal branch of the left anterior descending artery was then probed with a 0.014 inch thick guide wire, and catheterised with a 1.5 mm angioplasty balloon catheter; 5 ml of absolute alcohol was then slowly injected into the septal artery. After the procedure, the pressure gradient decreased from 140 mm Hg to 50 mm Hg.

On the fifth postoperative day, echocardiographic studies were carried out again. A reduction in the pressure gradient remained, and new wall motion dyskinesia could be seen in the basal septum. We performed myocardial contrast echocardiography with ECG triggered end diastole harmonic power Doppler technique using intravenous Levovist (a saccharide based transpulmonary echo contrast agent; Schering AG) before and after PTSMA. The preoperative image demonstrated homogeneous myocardial opacification (left). In contrast, the postoperative image showed the contrast defect at the basal septum which was consistent with ^{99m}Tc- MIBI myocardial perfusion imaging (right).

PTSMA is an effective procedure for some HOCM patients who are symptomatic despite sufficient drug treatment. We suggest that myocardial contrast echocardiography using the ECG triggered harmonic power Doppler technique is useful for detecting ablated septal myocardium, as well as scintigraphy.

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